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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/675,884	09/29/2003	Andrew Arthur Berlin	42P14241X	6824

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LISA A. HAILE, Ph.D.
ATTORNEY FOR INTEL CORPORATION
Suite 1100
4365 Executive Drive
San Diego, CA 92121-2133

EXAMINER	
GAKH, YELENA G	

ART UNIT	PAPER NUMBER
1743	

DATE MAILED: 12/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/675,884	BERLIN ET AL.	
	Examiner	Art Unit	
	Yelena G. Gakh, Ph.D.	1743	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 October 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. RCE and Amendment filed 10/13/05 are acknowledged. Claims 1-33 are cancelled. Claims 34-62 are pending in the application.

Response to Amendment

2. Double patenting rejection is withdrawn. All other objections and rejections are sustained.

Drawings

3. Amended Figure 1 is still objected as not being clear. As it was indicated in the previous Office actions, while irradiation of the sample can be an active step of the method, "scattering" radiation and "resonating" scattered radiation, also presented as the active steps of the method, cannot be considered as such. Scattering of the radiation is an intrinsic feature of the sample, and cannot be imposed on the sample.

Figure 4 is not clear as to whether it represents Raman spectra obtained by the inventive method, or it demonstrates conventional Raman spectra of four nucleotides. If these are known Raman spectra, Figure 4 should be marked as "prior art". From the specification it follows that Raman spectra represented by Figure 4 serve as the basis for determining wavelengths, which can be used for constructing the resonance chamber of the inventive method. From this except (page 15 [0039] of the specification) it follows that Raman spectra depicted on Figure 4 are indeed obtained by the conventional Raman spectroscopy, and therefore are not inventive.

The same uncertainty exists for Figures 16-21.

Specification

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The specification is objected to as not containing "a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art" to practice the method in its best mode.

The specification appears to be a mix of discussion of the prior art and well-known theoretical concepts of various forms of Raman spectroscopy along with disclosing possible structures of resonant chambers for different Raman techniques based on these theoretical concepts. According to the specification the chambers can be adapted for analysis of plural molecules and single molecules, including nucleotides of DNA. However, no ways of preparing samples containing single molecules of DNA (not mentioning single molecules of nucleotides) are disclosed in the specification, which makes it unclear, on how such samples can be prepared. The only real experiments represented in the specification refer to standard spontaneous Raman spectroscopy of four nucleotides, which cannot be considered inventive features of the method, since this technique is well known in the art.

The language and structure of the specification disclosing variety of possible embodiments of Raman techniques along with the resonance chambers together with known methods of the prior art makes it difficult to understand the inventive features of the method and system disclosed. The definition "resonance enhanced stimulated Raman spectroscopy" is not represented in such clear terms so as to differentiate it from stimulated "surface-enhanced resonance Raman scattering" (SERRS), the application of which for detection of single DNA molecules is also well known and documented (see e.g. Graham et al., Anal. Chem., 1997). The same is true for the definition of "resonant spectroscopic analysis chamber", which is not clear from the specification. Referring to Figure 15 (page 3), which "shows an exemplary apparatus and method for nucleic acid sequencing" by all possible Raman spectroscopy techniques, i.e. SERS, SERRS, CARS, and "resonance enhanced Raman spectroscopy" raises a question of how can all these different methods be performed with the same apparatus?

It seems that constructing the inventive spectroscopic system for performing the claimed method depicted on Figures 5 and 6 requires preliminary knowledge of exactly the same parameters that are supposed to be obtained by the method, e.g. "a wavelength of an inelastically scattered radiation of a molecule of interest" (page 16). This makes it unapparent how such system can be constructed.

It is unclear, if coherent anti-Stokes Raman spectroscopy (CARS) for detecting molecules requires a specific device or specific experiment set-up. What is disclosed on page 25 is a conventional CARS.

Furthermore, the only other examples of real Raman experiments shown on Figures 16-21 refer to SERS technique, which is well known and documented as the method for detecting single DNA molecules. The examples make it unclear, if SERS is considered one of the embodiments of the instant method. Figure 4 refers to "Stokes Raman spectra for dilute aqueous solutions of four DNA nucleotides, according to embodiments of the invention". However, it is not clear, which specific embodiments are meant here, and hence which specific Raman spectroscopy experiments Figure 4 illustrates. Moreover, SERS experiments require specific substrate, which is not disclosed in the specification, and is not mentioned in describing the resonance chamber, which makes completely unclear as to how the SERS experiments can be performed in the chamber of the invention.

Thus, it is not clear, which specific inventive features of Raman spectroscopy are disclosed in the specification, and which specific devices are required for performing different Raman techniques.

In conclusion, the specification is written in such a vague language regarding the inventive features of methods and apparatus for detecting molecules by resonance-enhanced Raman spectroscopy, with non-apparent embodiments of detecting enhanced resonances of different molecules placed in the same resonance chamber by "selectively" irradiating them at their resonance frequency, which is supposed to be unknown, and enhancing the resonance by constructing the resonance chamber, which geometry is based on the same unknown resonance frequencies, that it is difficult to apprehend the essence of the invention.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 34-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Nature of the Invention. The invention is directed to differentiating between target molecules on the basis of their Raman spectra obtained by enhancing inelastic scattered radiation of each molecule implying a novel resonant chamber comprisinh a resonance microcavity. The microcavity is supposed to be constructed such that it could enhance the intensity of the resonating inelastically scattered radiation for at least two different target molecules. The specification does not indicate, how it is possible to construct the microcavity for a plurality of different molecules having different vibration energies, when the geometry of the cavity depends on particular energies of particular molecule, and furthermore, with the same microcavity being capable of enhancing scattered radiation of two different molecules in sequence.

The State of the Prior Art. In a review article "Optical microcavities" (Nature, 2003) Vahala indicates "like its acoustic analogue the tuning fork, the optical microcavity (or microresonator) has a size-dependent resonant frequency spectrum" (page 839). With a plethora of references cited, Vahal covers the field including "strong-coupling cavity quantum electrodynamics" (page 839), "enhancement and suppression of spontaneous emission" (page 841), as well as various methods of constructing resonance microcavities (page 843). Vahala does not indicate any possibility of detecting an amplified inelastic scattering radiation of an unknown molecule using the optical microcavities, not mentioning selectively irradiating molecules, with different and uknown resonance

frequencies, in order to detect enhanced resonance of each of the molecules in sequence. Martini (see above) teaches "molecular Raman effect in the optical microcavity: QED vacuum confinement of an inelastic quantum scattering process" (Title) for the known vibration states of benzene, with a fine tuning of a geometry of the microcavity to fit parameters of benzene obtained by rigorous calculation. No way of detecting "the transmitted amplified inelastically scattered radiation" even for an unknown molecule utilizing the optical microcavity is indicated by Martini. Even less success can be expected for enhancing the resonance of different unknown frequencies in the same resonance microcavity on the basis of Martinis teaching. While Martini finely tunes microcavity geometry specifically to enhance **known** frequencies of a single species, i.e. benzene molecule, the instant application claims that the microcavity of the invention can enhance the resonances of unknown molecules, and to do this for different unknown molecules separately and in sequence. The specification is completely silent as to how it is done. Norris et al. ("Probing Single Molecules with Whispering Gallery Modes of Microspheres" at stanford.edu/mourner/pumping) indicate, "cavity quantum electrodynamics (CQED) predicts that the spontaneous emission rate of a single molecule can be strongly enhanced of the molecular transition is in resonance with a small, low-loss, optical cavity (or microcavity). This enhancement has been observed in atomic beans, in solutions, and in semiconductors. Experiments on a single molecule such as pentacene or terrylene would extend CQED measurements to a single quantum system embedded in a sold, in which the molecule is fixed spatially and can be studied for long periods. For these experiments spherical microcavities are particularly convenient resonators". The instant disclosure is silent regarding fixing molecules in the resonance microcavity for the time period long enough in order to perform all the steps of the method. Moreover, possible materials listed for the resonance chamber and channels are not relevant to the substrates used for surface-enhanced Raman spectroscopic analysis, which makes it non-apparent as to how such chamber can be used for SERS.

Thus, the prior art does not predict any possibility of *selectively resonating* inelastically scattered radiation, when the scattered radiation of the molecule is not known even for one molecule, not mentioning different molecules with different scattered

radiation frequencies. The prior art demonstrated a necessity of a fine tuning of the microcavity geometry for obtaining enhanced scattered radiation for molecules with well known Raman spectral parameters. The specification does not demonstrate, how such enhancement can be obtained for different molecules with unknown resonance frequencies. The well-known prior art discloses Raman enhanced spectroscopy of single DNA molecules and fragments using solid surfaces for attaching single molecules to the surface (see Ishikawa et al. "Single-Molecule Imaging and Spectroscopy Using Fluorescence and Surface-Enhanced Raman Scattering", J. Biol. Phys., 2002). No possibility of selective irradiating one molecule after another, which are contained in a solution and detecting enhanced scattered radiation for each of them by using the microcavity is indicated in the prior art.

The examiner still does not understand, which experiments demonstrate the present invention? The only spectra depicted on Figure 4 and 16-21 are referred in the specification as being conventional SERS spectra, well known in the art. The inventive "resonance enhanced stimulated Raman spectroscopy" (RESRS), which is principally different from SERS method, is not indicated as being performed. The examiner kindly requests the applicants to provide experimental material, including photographs of the resonance chamber in which the experiments were performed, and RESRS spectra obtained with such chamber. This experimental evidence will overcome rejections based on enablement requirements. Since the prior art does not predict any success in the method disclosed in the instant application, the rejections are sustained.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The issues of improper recitation of the active method steps such as "selectively resonating inelastically scattered radiation" and "transmitting the amplified radiation" were addressed in the previous Office actions and remain valid.

Response to Arguments

9. Applicant's arguments filed 10/13/05 have been fully considered but they are not persuasive. Most of the Applicants' arguments were addressed in the previous sections of the present Office action. The examiner just would like to emphasize that she strongly disagrees with the Applicants' statement that "the enablement requirement does not require that the specification of an applications explicitly teach each and every aspect of a claimed invention". If the Applicants consider their invention so novel that the prior art provided by the examiner does not predict any success of such method and does not give any guidance for the routineer in the art to perform the method, and when the working examples are referred in the specification to the well known method (SERS), rather than the inventive method RESRS, then the Applicants are required to provide all details of the invention, which are essential for its performance.

The examiner expects an adequate response of the Applicants to all issues raised by the examiner.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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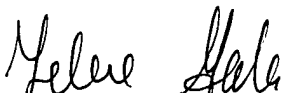

YELENA GAKH
PRIMARY EXAMINER